

(fibrinogen, FII, FV, FVIII and vWF) and the anticoagulant factors (PC, PS, AT, PZ, PZI) have a large genetic component.

Estimates of heritability are population-specific and dependent on the prevalence of non-genetic determinants. A hypothetical example illustrating this point is that which has been given for phenylketonuria, an inborn error of metabolism in which phenylalanine accumulates in children who lack the enzyme phenylalanine hydroxylase, which converts dietary phenylalanine to tyrosine. In a population with a diet rich in phenylalanine in which some have the phenylketonuria defect, the disease will be purely genetic. By contrast, if there were a population in which everyone had the defect, but the phenylalanine content of the diet varied, the disease would be fully accounted for by environmental factors. Therefore, the size of heritability estimates cannot be simply compared across populations, or between analytes, and should be viewed qualitatively. However, if a trait has a sizeable heritable component, it is worthwhile trying to find the gene or genes that influence it.

In the study reported today, Ariëns and colleagues go beyond assessing the heritability of clotting factors to estimate that of markers of clotting activation. This approach derives from work of Bauer and Rosenberg in the 1980s, who postulated a prothrombotic state characterised by an increased level of coagulation-system activation and thrombin production in individuals with an increased risk of thrombosis.^{8,9} This prothrombotic state (sometimes called the prothrombotic state) is assessed by measuring activation peptides released when clotting factors are activated (prothrombin fragment 1+2, fibinopeptide A), proteolytically degraded (D-dimer), or inactivated by formation of complexes with anticoagulant proteins (thrombin-antithrombin complex). Ariëns and colleagues found all these peptides and complexes to have a high heritability. This finding may be directly relevant to thrombotic risk, since a recent report has shown that D-dimer concentrations are associated with the risk of venous thrombosis.¹⁰ A study of clotting-factor heritability in a large French-Canadian kindred showed similar findings for the heritability of measures of protein C activation (protein C activation peptide) and inactivation (complex of activated protein C with C inhibitor and complex of activated protein C with α_1 -antitrypsin).⁷ Thus, the net thrombohaemorrhagic balance seems to be genetically influenced to a significant degree for both activation and inactivation of the haemostatic mechanism. As Ariëns and colleagues point out, the increased activity of the coagulation system may be due to raised concentrations of clotting factors, or perhaps to common genetic or environmental factors that influence activation of different clotting factors. These studies imply that future research into the genetics of thrombosis should follow two paths: into the genetic basis of raised concentrations of clotting factors, and into the genetic basis of the prothrombotic state.

*F R Rosendaal, E G Bovill

*Department of Clinical Epidemiology and Haematology, Leiden University Medical Center, 2300 RC Leiden, Netherlands; and Department of Pathology, University of Vermont, Burlington, VT, USA (e-mail: f.r.rosendaal@lumc.nl)

- 1 Virchow R. Phlogose und Thrombose im Gefäßsystem. Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt: Staatsdruckerei; 1856.
- 2 Åstrup T. The haemostatic balance. *Thromb Diath Haemorrh (Stutt)* 1958; **2**: 347–57.
- 3 Rosendaal FR. Risk factors for venous thrombotic disease. *Thromb Haemost* 1999; **82**: 610–19.

- 4 Kamphuisen PW, Houwing-Duistermaat JJ, van Houwelingen JC, Eikenboom JCJ, Bertina RM, Rosendaal FR. Familial clustering of factor VIII and von Willebrand factor levels. *Thromb Haemost* 1998; **79**: 323–27.
- 5 de Lange M, Snieder H, Ariëns RA, Spector TD, Grant PJ. The genetics of haemostasis: a twin study. *Lancet* 2001; **357**: 101–05.
- 6 Souto JC, Almasy L, Borrell M, et al. Genetic determinants of hemostasis phenotypes in Spanish families. *Circulation* 2000; **101**: 1546–51.
- 7 Rosendaal FR, Hasstedt SJ, Bauer K, et al. Heritability of clotting factors, coagulation inhibitors and activation peptides. *Blood* 2001; **98**: 789.
- 8 Bauer KA, Rosenberg RD. The pathophysiology of the prothrombotic state in humans: insights gained from studies using markers of hemostatic system activation. *Blood* 1987; **70**: 343–50.
- 9 Teitel JM, Bauer KA, Lau HK, Rosenberg RD. Studies of the prothrombin activation pathway utilizing radioimmunoassays for the F2/F1 + 2 fragment and thrombin-antithrombin complex. *Blood* 1982; **59**: 1086–97.
- 10 Andreescu ACM, Cushman M, Rosendaal FR. D-Dimer as a risk factor for venous thrombosis: the Leiden Thrombophilia Study. *Thromb Haemost* 2002; **87**: 47–51.

Maternal deaths among Afghan refugees

See page 643

Female refugees face special risks.¹ Women have difficulty in access to refugee health services, in receiving food and commodities, and in obtaining protection from sexual violence.² Being pregnant and Afghan compounds these risks. Through the UN High Commissioner for Refugees (UNHCR), the Women's Commission for Refugee Women and Children, and others, there is now wide awareness of the risks and needs of women and girls. Yet in environments unfavourable to women it has proved difficult to translate this awareness into effective programmes.

In today's *Lancet*, Linda Bartlett and colleagues report crude mortality and maternal mortality data from 12 Afghan refugee settlements housing 134 406 refugees in the Hangu area of Pakistan's Northwest Frontier Province. They counted 1197 deaths in 1999–2000, and calculated a crude mortality rate of 5.5/1000. Of the 66 deaths among women of reproductive age, 27 (41%) were due to maternal causes. For this refugee population the maternal mortality ratio was 291/100 000 livebirths, higher than that for Pakistan (200) but far lower than the 820 estimated for Afghanistan.

Reasons for preventable maternal deaths fall into three categories, sometimes called the three delays or barriers to emergency obstetrical care.³ Barriers were identified in 22 of the 27 maternal deaths in this study, and these 22 had a total of 39 barriers. 18 women had barriers in the category of household awareness and decision-making, seven in transport to a referral hospital, and 14 in receiving appropriate care after reaching the facility.

Although antenatal services are provided to refugees at primary-health-care clinics, most refugee women give birth at home, attended by relatives and sometimes traditional birth attendants. Refugee settlements commonly have community health workers, whose duties include health promotion and care for sick children and pregnant women. Many Afghan refugee community-health workers are male and may spend much of their time out of the settlement looking for work. The female community workers who could provide the education and care needed are usually not empowered to move far beyond their own household. For cultural reasons it is not surprising that in the Hangu settlements the largest number of barriers existed at the household-decision level. Transportation barriers formed a smaller number. Where refugees are spread over a wide area, communication and coordination of emergency

transportation to the referral facility is almost invariably a problem.

In many developing countries, the first referral hospital is a neglected part of the health system, under-resourced, understaffed, and with its personnel demoralised.⁴ This level of the formal health system is commonly the one most affected by the refugee influx. Although relief organisations try to compensate for the load imposed by refugees, the assistance provided is seldom commensurate with the burden. The estimated 3 million Afghan refugees in Pakistan impose a substantial demand on the country's health system. Half of this number do not live in organised settlements where there are non-governmental organisations to provide primary health care.

With refugees competing with their hosts in business and labour markets, and with assistance provided to refugees but not hosts, tensions inevitably arise. The flow of weapons that follows many refugee migrations may further destabilise a region. Host governments may openly blame refugees for social and economic problems, often instituting forced returns to dangerous situations. When refugee women present for emergency obstetric care to host-country hospitals, these negative perceptions, added to language and cultural barriers, can result in second-class treatment. However, in some circumstances, integration of refugee and host-country health systems has improved obstetric services and transport provisions for both populations.⁶

The data reported today from the 12 refugee settlements in Hangu deserve scrutiny. A crude mortality rate of 5.5/1000 is extraordinarily low. The comparable figure for Pakistan is 11 and for Afghanistan is 19, although a small study inside Afghanistan in April, 2001, found an appalling crude mortality rate of 95.^{7,8} It is possible that an exceptional level of health care was provided to the Hangu settlements, or that there was a favourable age-structure to the refugee population (not given in the article). More likely, deaths were under-reported, a common situation in settlements where movements in and out are usual.⁹ Although the maternal mortality ratios are similar to the Pakistan figures, maternal death ratio⁵ are notoriously hard to measure, especially in small populations.¹⁰ Figures for crude mortality and maternal mortality usually follow one another, which again suggests that some deaths were missed.

The challenge of returning refugees and the internally displaced to their homes in Afghanistan is great, and the challenge of rebuilding health care formidable.¹¹ Despite the seemingly vast sums of aid funds pledged for Afghanistan, there is a real danger that, without effective health-sector coordination, assistance can be dissipated and only modest long-term impact realised. Although many relief organisations are preparing to meet the immediate needs within Afghanistan, the less glamorous and ultimately more arduous task of rebuilding national capacity must always remain the clear goal. This opportunity to create a health system free of past inequities that will make the country safe for women and children must not be lost.^{12,13}

Gilbert Burnham

Johns Hopkins Bloomberg School of Public Health, Center for International Emergency, Disaster and Refugee Studies, Baltimore, MD 21205, USA
(e-mail: gburnham@jhsph.edu)

- 1 Guidelines on the protection of refugee women. Geneva: UNHCR, 1991.
- 2 Rojnik B, Andolsek-Jeras L, Obersnel-Kveder D. Women in difficult circumstances: war victims and refugees. *Int J Gynecol Obstet* 1995; **48**: 311–15.

- 3 United Nations Population Fund. Update 1998–99 Maternal Mortality. New York: UNFPA, 2000.
- 4 Van Lerbergh W, de Bethune X, de Brouwere V. Hospitals in sub-Saharan Africa: why we need more of what does not work as it should. *Trop Med Intl Health* 1997; **2**: 799–808.
- 5 Muggah R, Berman E. Humanitarianism under threat: the humanitarian impacts of small arms and light weapons. <http://www.smallarmssurvey.org/SpecialReports.html> (accessed on Feb 28, 2002).
- 6 Van Damme W, De Brouwere V, Boelaert M, Van Lerberghe W. Effects of a refugee-assistance programme on host population in Guinea as measured by obstetric interventions. *Lancet* 1998; **351**: 1609–13.
- 7 2001 World Population Data Sheet. Washington DC: The Population Reference Bureau, 2001
- 8 Assefa F, Jabarkhill M, Salama P, Spiegel P. Malnutrition and mortality in Kohistan district, Afghanistan, April 2001. *JAMA* 2001; **286**: 2723–28.
- 9 Spiegel PB, Sheik M, Woodruff BA, Burnham G. The accuracy of mortality reporting in displaced persons camps during the post-emergency phase. *Disasters* 2001; **25**: 172–80.
- 10 Hill K, AbouZahr C, Wardlaw T. Estimates of maternal mortality for 1995. *Bull World Health Organ* 2001; **79**: 182–93.
- 11 Macrae J. Dilemmas of legitimacy, sustainability, and coherence: rehabilitating the health sector. In: Kumar K, ed. *Rebuilding civil societies after civil war: critical roles for international assistance*. Boulder, CO, USA: Lynne Rienner, 1997: 183–99.
- 12 *The Lancet*. Reconstruction of health care in Afghanistan. *Lancet* 2001; **358**: 2009.
- 13 Rasekh Z, Bauer HM, Manos M, Iacopino V. Women's health and human rights in Afghanistan. *JAMA* 1998; **280**: 449–55.

The expanding diversity of rotaviruses

The recognition of rotaviruses as major causes of acute gastroenteritis in infants and young children, and of the need to develop effective vaccines to protect against severe rotavirus disease, has stimulated efforts to describe their antigenic and genomic diversity.¹ Rotaviruses possess a segmented, double-stranded RNA genome, with each of the 11 segments encoding at least one structural or non-structural protein. The mature rotavirus particle has three layers (figure). On the basis of the antigenic specificity of the middle capsid protein, virus protein 6 (VP6), human rotaviruses are classified into three groups (A–C, of which group A causes most childhood infections). Group A rotaviruses can in turn be classed into two main VP6 subgroups (I and II). The two structural proteins that comprise the outer viral capsid, VP7 and VP4, are the neutralisation antigens defining VP7 (or G, for glycoprotein) and VP4 (or P, for protease-sensitive) serotypes.²

Early studies in the 1980s that investigated the molecular epidemiology of group A rotaviruses used polyacrylamide gel electrophoresis to discriminate between rotavirus strains. Differences in the relative migration pattern of RNA segment 11 could differentiate “short” from “long” profiles, with occasional strains possessing “super-short” profiles. More subtle differences in the migration of other segments were used to further discriminate between strains (“electropherotypes”). Most group A rotaviruses possessed particular constellations of electropherotype, subgroup, and G serotype, and RNA hybridisation studies indicated that they belonged to one of two “gene families”, or genogroups, named after their prototype strains Wa and DS-1.^{3,4} Accordingly, short electropherotype, subgroup I rotaviruses were of serotype G2 (DS-1-like), and long electropherotype, subgroup II rotaviruses were of serotype G1, G3, or G4 (Wa-like). Some strains, however, exhibited features belonging to both genogroups.⁵ In the late 1980s and early 1990s, molecular genotyping techniques (reverse-transcriptase PCR and probe hybridisation) were developed to examine the genes encoding the